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Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients

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Background. Patients with end-stage renal disease (ESRD) are at increased risk of cardiovascular mortality and morbidity. Many complications arise in ESRD patients as a result of the twin arterial pathologies of atherosclerosis and arteriosclerosis. Part of this latter process is calcification of the arterial media, which is thought significantly to increase vascular stiffness. The aim of our study was to explore the relationship between measures of arterial stiffness—pulse wave velocity (PWV)—and the extent of calcification in the coronary arteries (CAC).

Methods. Over a period of 2 years 82 patients from our renal unit were invited to participate in our study. Sixty-two patients agreed to undergo electron beam computerized tomography (EBCT), and in 55 (38 males and 17 females), PWV measurements were made. EBCT and PWV measurements were done according to previously described protocols.

Results. The mean age of the 55 patients was 56.4 years. The mean duration of dialysis was 65.4 months, and the mean CAC score was 2551. The mean PWV was 9.13 m/s. PWV strongly correlated with total CAC even after correction for age, dialysis duration, and time averaged C-reactive protein (CRP) ($P = 0.0001$). CAC scores were significantly different when compared according to PWV tertiles ($P = 0.0001$).

Conclusion. We have demonstrated that PWV is strongly related to the degree of EBCT-derived coronary artery calcium score in chronic kidney disease patients.

Patients with end-stage renal disease (ESRD) are at increased risk of cardiovascular mortality and morbidity. Clinical and epidemiologic studies have shown that structural and functional changes in conduit arteries are a major contributing factor to the high mortality in uremic patients. Macrovascular complications caused by atherosclerosis are increased in prevalence and speed of onset in ESRD patients. These are partly responsible for the high incidence of ischemic heart disease, congestive heart failure, sudden death, and stroke [1]. Of equal or greater importance, however, are arteriosclerosis and arterial stiffening [2], because they are prime determinants of left ventricular hypertrophy and patient survival on dialysis [3].

Reasons behind increased arterial stiffness in ESRD are not fully understood, but it is believed that vascular (medial) calcification is a major contributing factor. Guerin et al, using a semiquantitative assessment based on a B-mode ultrasound-derived score calculated according to the number of arterial sites with calcifications, demonstrated in ESRD patients that the presence of mural vascular calcifications in large arteries of hemodialysis patients was associated with increased pulse wave velocity (PWV) (arterial stiffness) [4]. Subsequently, the same group demonstrated prospectively that both the increased arterial stiffness [5] and the presence of large-artery calcification [6] were major predictors of all-cause and cardiovascular mortality in chronic kidney disease patients.

Only recently, with techniques such as electron-beam computerized tomography (EBCT), has it been possible to accurately and quantitatively assess coronary artery calcification (CAC).

In the general population, such CAC scores are strongly predictive of coronary artery atherosclerosis and of future major adverse cardiac events [7]. The phenomenon of CAC has been much reported in ESRD patients over the last 7 years. It has increased enormously in dialysis patients [8], and also appears at a younger age [9] and progresses rapidly [10]. However, unlike arterial stiffness, its prognostic significance in ESRD remains to be determined.

In order to explore potential implications of CAC we studied the relationship between direct measures of large-artery stiffness with prognostic value in ESRD patients (aortic PWV) and coronary artery calcification measured with a reproducible and accurate method (EBCT) [11, 12].

Key words: coronary artery calcification, pulse wave velocity, arterial stiffness.

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Table 1. Patient characteristics

	N Valid	Mean	SE mean	Median	SD	Minimum	Maximum
Age *years*	55						
Weight *kg*	55	68.7	1.8	66	13.3	39	103
Dialysis duration *months*	48	65.4	12.8	24	88.8	1	372
Aortic PWV *m/s*	55	9.1	.2	9	1.5	5.9	12.3
CAC total score	55	2551.1	373.8	1640	2772.5	0	11538
Time-averaged CRP *mg/L*	55	19.6	3.3	12	23.8	1	151
Albumin *g/L*	55	34.9	.5	35	4.0	27	43
Cholesterol *mmol/L*	55	4.8	.2	5	1.1	2	8
Time-averaged calcium *mmol/L*	55	2.4	0	2	.1	2.2	2.7
Time-averaged phosphorus *mmol/L*	55	1.6	0	1	.3	1.0	2.5
Calcium-phosphorus ion product $mmol^2/L^2$	55	3.7	.1	4	.8	2.25	5.52
SBP *mm Hg*	55	145.4	3.9	142	28.9	90	219
DBP *mm Hg*	55	73.9	1.8	70	13.1	50	104
Pulse pressure *mm Hg*	55	71.3	3.1	67	23.0	40	123

Abbreviations are: PWV, pulse wave velocity; CAC, coronary artery calcification; CRP, C-reactive protein; SBP, systolic blood pressure; DBP, diastolic blood pressure.

METHODS

Study subjects

Over a period of 2 years (May 2001 to May 2003), 82 patients from our renal unit were invited to participate in a study trying to find a relation between PWV and EBCT-generated CAC. Sixty-two patients agreed to undergo EBCT, and of these, 55 (38 males and 17 females) underwent measurement of aortic PWV within 3 months of EBCT. Only these 55 patients' results have been analyzed. All of the studied patients had renal impairment—26 were on hemodialysis, 4 on continuous ambulatory peritoneal dialysis, 7 had chronic kidney disease not requiring dialysis, and 18 were postrenal transplantation.

The causes of renal failure in the 55 patients were glomerulonephritis in 18, diabetes in 17, Alport's syndrome in 9, renovascular disease in 3, polycystic kidney disease in 4, and reflux nephropathy and hypertension each in 2 patients.

A database was constructed including baseline demographic and laboratory data from the information on the Renal Unit computer database for each patient. These included height and weight at the time of EBCT, systolic and diastolic blood pressure, time-averaged systolic and diastolic BP values (average of all the blood pressure readings of the patients during their follow-up period), the duration of chronic renal disease; mean levels for calcium, phosphorus, calcium-phosphorus product, albumin, total nonfasting cholesterol and C-reactive protein (CRP) were derived from 12 to 84 months of routine biochemical information for all 55 patients (see Table 1). The median number of blood test values for each patient was 49 (range 12 to 396). A complete dataset was compiled for each patient. Medication charts for the preceding (1 to 8) years on dialysis were reviewed to calculate the daily dose of calcium-containing phosphate binder, and the total cumulative exposure to calcium-containing oral phosphate binders.

Protocol of electron-beam CT

All subjects underwent electron-beam computed tomography (CT) at the Imatron Unit, Royal Brompton Hospital, on a C-100 scanner (Imatron; South San Francisco, CA, USA) [11]. Images were performed with 100-ms scanning time, and a single slice thickness of 3-mm. Thirty-six to 40 tomographic slices were obtained for each subject during two breath-holding sessions. Tomographic imaging was electronically triggered at 40% of the R-R interval to minimize cardiac movement, and proceeded from the carina to the diaphragm. The intra-assay coefficient of variation for the scoring was <5%.

The acquired images were scored with the use of Imatron software by a single radiologist blinded to the clinical or angiographic history of the patient. As originally described by Agatston [11], the degree of coronary artery calcification was calculated by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion to yield a lesion-specific calcification score. The sum of the scores of all arterial lesions was used for analysis.

Pulse wave velocity protocol

A carotid and a femoral artery waveform were obtained consecutively using the SphygmoCor apparatus (PWV, Inc., Westmead, Australia) and customized software. Using an ECG gated signal and anthropometric distances, the PWV was derived using methodology previously described and validated [13, 14].

The intraobserver error for PWV was determined in 20 young healthy volunteers (−3.5%); in 10 dialysis patients (−4.7%); and in 10 renal transplant patients similarly studied (−3.8%). When the intraobserver reproducibility was assessed with a 4-hour gap between readings, at rest, and without dialysis or hemodynamic drugs, the intra-observer error was 5.8% [14]. All the measurements were made by a single operator.

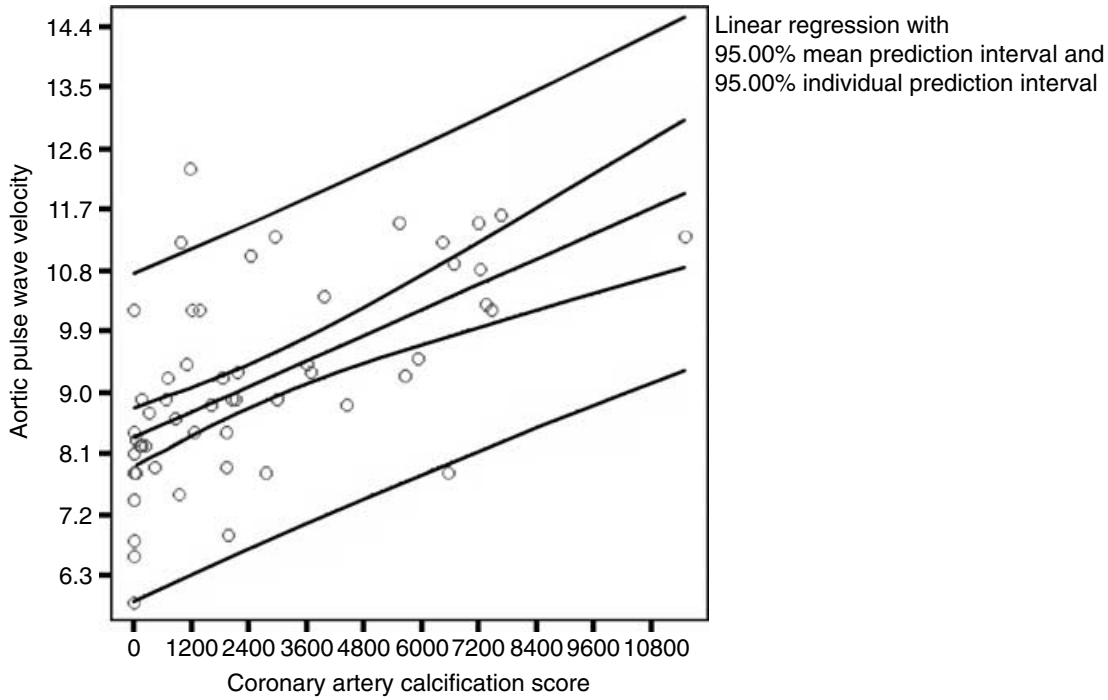

Fig. 1. Scatter plot of pulse wave velocity (PWV) and coronary artery calcification (CAC) score.

Statistical analysis

All values are expressed as mean ± standard error unless stated in the text. Spearman's rho correlation (non-parametric) coefficient was used for bivariate correlation calculations. Bivariate partial correlations were used to correct for possible confounders. A multiple linear regression analysis was also used to examine associations between PWV and CAC adjusted for possible confounders. The square root transform of CAC score was used to normalize the data. Comparisons between groups were made using the Mann-Whitney test. Kruskal-Wallis test was used to compare more than two not normally distributed means. A P value of < 0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

Baseline characteristics of the patients are outlined in Table 1. The mean age of the 55 patients was 56.4 ± 14.1 (SD) years (range 21 to 80). There were 17 females and 38 males. The mean duration of dialysis was 65.4 months (median 24, range 1 to 372), and the mean CAC score was 2551 ± 373.8 (median 1640, range 0 to 11,538). The mean PWV was 9.13 ± 0.19 m/s (median 8.9, range 5.9 to 12.3).

Pulse wave velocity correlations (Spearman's rho)

Pulse wave velocity strongly correlated with total CAC ($P = 0.0001$ $r = 0.65$) (see Fig. 1). PWV also positively correlated with patient age ($P = 0.0001$, $r = 0.592$), dialysis duration ($P = 0.037$, $r = 0.303$), and time-averaged CRP ($P = 0.028$, $r = 0.301$), but not with time-averaged plasma phosphate, plasma calcium, calcium-phosphorus ion product levels, or with the total cumulative exposure to calcium-containing oral phosphate binders. PWV was slightly higher in men than women (mean 9.37 and mean 8.56, respectively, $P = 0.06$). Pulse wave velocity was not associated with systolic blood pressure, but was inversely associated with diastolic pressure ($P = 0.005$, $r = -0.37$). CAC was also inversely associated with DBP in this population ($r = -0.44$, $P = 0.0007$).

It is well known that both vascular stiffness and CAC increase with age and duration of dialysis [3, 15] and inflammation [16], and they also vary with sex and diastolic BP. The age- and sex-adjusted partial correlation between CAC and PWV was $r = 0.46$. Further adjustment for dialysis duration, time-averaged CRP, and diastolic blood pressure reduced this to a partial correlation ($r = 0.31$). In a multiple linear regression analysis PWV was significantly associated with CAC ($P = 0.001$), and remained so on adjusting for age, sex, dialysis duration, time-averaged CRP, and diastolic blood pressure ($P = 0.03$). Mode of dialysis and transplantation status had no impact on measured PWV.

Coronary artery calcifications and pulse wave velocity tertiles

To further dissect the relationship between increased coronary artery calcification scores and increased

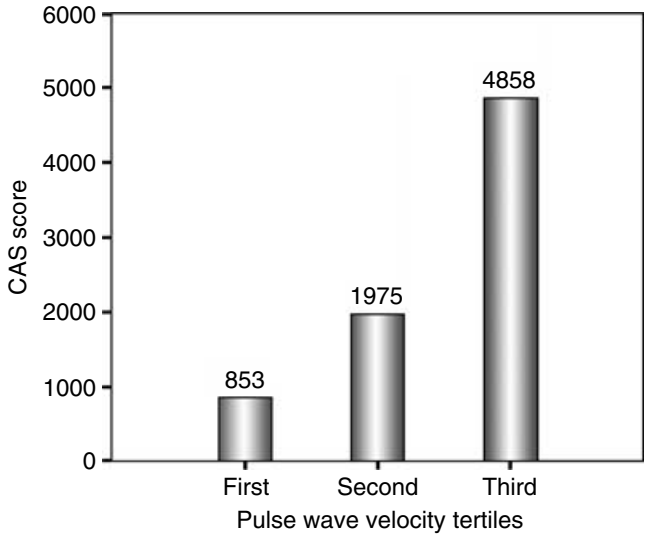

Fig. 2. Bar chart showing pulse wave velocity (PWV) tertiles and coronary artery calcification (CAC) scores.

aortic stiffness, we divided the study population into PWV tertiles. The first tertile (PWV range 5.9 to 8.35) had a mean CAC of 853, the second tertile (PWV range 8.36 to 9.4) had a mean CAC of 1975, and the third group had a mean CAC of 4858 (PWV range 9.41 to 12.3) (see Fig. 2). Comparison of the three means using Kruskal-Wallis test showed a statistically significant difference with $P = 0.0001$. Intermeans comparison (Mann-Whitney U test) again showed a statistically significant difference with a P value of 0.001 for the comparison of the first and second tertiles, and of 0.03 for the second and third tertiles comparison (see Fig. 2).

DISCUSSION

The result of our study demonstrated for the first time that increased arterial stiffening—measured as aortic PWV—is independently predictive of EBCT-derived CAC score in chronic kidney disease (CKD) patients. We demonstrated a close correlation between CAC and PWV ($r = 0.65$), even after correcting for confounders like age and dialysis duration, which might increase aortic stiffness [3]. We found that CAC strongly correlated with the tertiles of PWV, so that as PWV increased, CAC also increased proportionally ($P = 0.0001$).

We provide strong evidence to link conduit artery functional characteristics with the extent of accurately determined vascular calcification. This relationship was apparent after correcting for patient characteristics recognized as influencing both the calcification process and PWV: age, duration of dialysis, inflammation, and the prescribed dose of calcium-based phosphate binders [17]. The present findings are important because arterial calcification may be the only known preventable factor in the vicious circle of arterial stiffness/increased PWV in CKD patients.

Vascular abnormalities (structural and functional)—an almost invariable ESRD complication—have recently emerged as the most powerful predictors of a negative outcome in CKD populations. Three factors that have a complex inter-relationship include: arterial stiffness (elastic incremental modulus of the carotid artery), increased aortic PWV, and vascular (conduit artery) calcification. It has been demonstrated that total mortality increased by 39% with every 1 m/s increase in PWV [17, 18], 1.9 times an increase in all-cause mortality hazard ratio for each unit increment in calcification [6], and 1.6 times an increase in all-cause mortality for each standard deviation increase in carotid artery elastic modulus [6].

Although a link between vascular stiffness and calcification is suspected, the few previous studies in the literature correlating arterial stiffness with calcification have used (at best) semiquantitative B-mode ultrasound or plain x-ray imaging [6] of the aorta and large muscular-elastic arteries (carotid, femoral); neither of these two imaging techniques is optimal to detect and quantify vascular calcification. The most accurate and reproducible vascular calcification detection and quantification techniques involve CT scanning (most notably, EBCT scanning to derive a CAC score)[11, 12].

In the general population there is a complex relationship between BP and arterial stiffness. Increased SBP, reduced DBP, and widened pulse pressure are all associated with increasing arterial stiffness [14]. Important however, in this study the correlation between CAC and PWV was independent of BP after multivariate analysis. This strengthens the likely association between vessel structure and function.

The greatly increased CAC and its early onset and rapid progression [9] in dialysis, though remarkable, has an uncertain significance. Our study directly links this easily defined cardiac parameter with a validated, prognostically important functional vessel characteristic (PWV). Previous studies have shown a tight correlation between the degree of coronary and aortic calcifications, and that they are closely linked also in terms of risk factors for progression [10, 19]. Furthermore, a new avenue is open to exploration: it is possible that the increased aortic stiffness places a higher burden on the coronary endothelium (higher endothelial stress), initiating a process of accelerated atherosclerosis and calcification at this level that will translate into higher rates of ischemic heart disease compared with nonrenal subjects.

Limitations of this study include case-mix and renal replacement therapy-mix diversity, small patient numbers, and a large spread of patient dialysis exposures. In order to ensure generalizability of these data, larger, single cohort (dialysis, transplanted) studies are required.

CONCLUSION

We now need a study, population-based or interventional, which is empowered to provide useful prognostic information that can address the progression or retardation of coronary and aortic calcification, and vessel functional changes in uremic subjects.

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